43. (Amended) A method for detecting the presence of a DNA molecule comprising SEQ ID NO: 223 in a biological sample, the method comprising:

(a) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein the oligonucleotide primers are specific for SEQ ID NO:223; and

(b) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers.

44. (Amended) The method of claim 43, wherein the oligonucleotide primers comprise at least about 10 contiguous nucleotides of SEQ ID NO:223.

45. (Amended) A method for detecting the presence of a DNA molecule comprising SEQ ID NO: 224 in a biological sample, the method comprising:

(a) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein the oligonucleotide primers are specific for SEQ ID NO:224; and

(b) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers.

46. (Amended) The method of claim 45, wherein the oligonucleotide primers comprise at least about 10 contiguous nucleotides of SEQ ID NO:224.

REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Certain pending claims in the present application have been amended for purposes of clarity and to expedite prosecution of this case to allowance. Following the amendments, claims 25-28

and 37-40 are cancelled and claims 23-24, 31-36 and 43-46 are pending. The currently pending claims are thus directed to detection methods employing primers that are specific for polynucleotides of SEQ ID NO:110 (P501S), SEQ ID NO:173-175 and 177 (P703 variants), SEQ ID NO:223 (P509S) and SEQ ID NO:224 (P510S).

It is urged that support for this amendment may be found throughout the specification as originally filed, and that none of the amendments constitute new matter or raise new issues for consideration. Rather, applicants submit this amendment, in large part, for purposes of placing the application in better condition for allowance and/or appeal. It should also be noted that the above amendment is made without prejudice to prosecution of any subject matter modified and/or removed by this amendment in a related divisional, continuation and/or continuation-in-part application.

Applicants wish to thank Examiner Davis for the productive interview conducted at the U.S.P.T.O. on August 20, 2001.

REJECTION UNDER 35 USC 101

Claims 25-34 and 37-46 stand rejected under 35 USC 101, as allegedly lacking a specific utility. Applicants note that the Examiner has not applied this rejection to pending claims 23-24 and 35-36, directed to methods of detection employing primers specific for a polynucleotide of SEQ ID NO:110 (also referred to as P501S).

Applicants previously submitted the Declaration of Raymond Houghton confirming the expected serum-based detection of expression of SEQ ID NO:110 (P501S) and SEQ ID NO:172-175 and 177 (P703P variants) in subjects bearing tumors expressing these sequences. The Examiner apparently accepts this declaration as supporting utility for SEQ ID NO:110, but contends that, "except for SEQ ID NO:110, it is unpredictable that the claimed sequences are expressed at higher levels in serum of patients with prostate cancer, as compared to normal healthy human."

Applicants respectfully traverse this rejection, for reasons already of record, and further in view of the issues addressed during the interview with Examiner Davis. As discussed, applicants have demonstrated prostate-specific, tumor-associated

expression profiles for the presently claimed sequences that more than adequately establish utility under 35 USC 101, as further clarified below.

Regarding the P703P sequences of SEQ ID NO:172-175 and 177, the Examiner asserts that although the sequences are prostate specific, "there is no correlation between SEQ ID NO:172-175 and 177 and prostate cancer." The Examiner further contends that although these sequences "are splice variants of P703P, wherein P703P is expressed at a higher level in blood of mice transplanted with prostate tumor as compared to normal mice, it is not necessary that splice variants are expressed in the same pattern as the wild type parent sequence."

The prior Declaration of Raymond Houghton clearly established that P703P-expressing tumor cells are detectable in a serum-based diagnostic assay. Moreover, as set forth in the attached Declaration of Davin Dillon, Ph.D., each of the P703P splice variants, e.g., SEQ ID NO:172-175 and 177, also exhibit prostate-specific expression profiles. More particularly, based upon multiple lines of evidence, the P703P splice variants identified by the applicants are expressed in prostate tumors and normal prostate tissue, but are not highly expressed in any other normal tissues. Thus, for reasons similar to those already established for P501S (SEQ ID NO:110), the P703P sequences of SEQ ID NO:172-175 and 177 also satisfy the utility requirements of 35 USC 101.

As for SEQ ID NO:223 and 224, page 27, lines 24-24, of the applicants' specification describes that these two clones, referred to as P509S and P510S, respectively, were found to be overexpressed in prostate tumor and normal prostate and expressed only at low levels in other normal tissues tested, including liver pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney ovary, lung, spinal cord, skeletal muscle and colon. Thus, SEQ ID NO:223 and 224, like SEQ ID NO:110, 172-175 and 177 discussed above, exhibit prostate-specific expression profiles, and, on this basis, would be reasonably expected by the skilled artisan to have specific diagnostic utility.

Applicants stress, however, that although they have demonstrated, for purposes of illustration, that P501S and P703P sequences having prostate-specific

expression are useful in the serum-based detection of circulating tumor cells expressing these sequences, applicants respectfully disagree with the position that it is therefore necessary to demonstrate serum detection of expression of every presently claimed sequence, e.g., SEQ ID NO:223 and 224, in order to satisfy utility under 35 USC 101. An important prognostic event that occurs during prostate cancer progression is the acquisition by tumor cells of the ability to become invasive, escape the site of the primary tumor and enter the circulatory system, where the tumor cells can then potentially colonize distant organ sites. Indeed, the presence of metastatic tumor cells that have entered the circulation and/or colonized organ sites distinct from the site of origin of the primary tumor generally results in a less favorable prognosis than is the case where tumor cells are contained within a single non-invasive lesion in a subject.

Prostate-specific sequences, such as those presently claimed, represent important tumor markers in this regard. As the claimed sequences do not exhibit substantial expression in normal tissues, detection of expression of the claimed sequences in, for example, a blood sample, would be understood by the skilled artisan to be indicative of the presence of circulating tumor cells in a subject. Such a finding is important diagnostically because it demonstrates that the subject from which the sample was obtained bears a primary prostate tumor that has become invasive and entered the circulation. Applicants acknowledge that the presently claimed methods may not conclusively demonstrate the presence and location of all metastatic lesions at non-prostate organ sites, as noted by the Examiner. However, the claimed methods are nonetheless useful in the detection of circulating tumor cells, and this too offers valuable diagnostic and prognostic information about the presence in a subject of an invasive prostate tumor.

In view of the above, one of ordinary skill in the art would understand and expect that each of the applicants' claimed sequences, including SEQ ID NO:223 and 224, possess specific, credible and substantial utilities on the basis of their prostate-specific expression patterns. Reconsideration and withdrawal of the Examiner's rejection under 35 USC 101 is thus respectfully requested.

REJECTIONS UNDER 35 USC 112

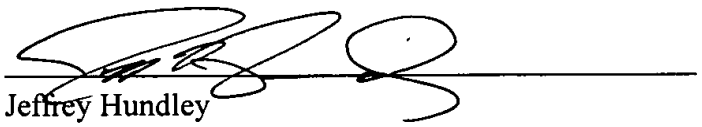
The Examiner rejects the pending claims under 35 USC 112, first and second paragraphs, for reasons already of record.

Applicants appreciate the helpful discussion with Examiner Davis regarding the standing 35 USC 112 rejections during the August 20 interview. As therein discussed, applicants have elected at this time to amend the pending claims, without prejudice, to specify that both primers employed in the claimed method are specific for polynucleotides of the claimed sequences. Applicants note that the above amendments are made for purposes of clarity and to expedite prosecution of the present application to allowance. Moreover, applicants specifically reserve the right to prosecute subject matter modified and/or removed by this amendment in a related divisional, continuation and/or continuation-in-part application.

Favorable reconsideration and allowance of the pending claims is respectfully requested. The Examiner is encouraged to contact the undersigned with any questions, concerns or suggestions pertaining to this communication.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC



Jeffrey Hundley
Registration No. 42,676

JEH:sds
Enclosures:
Postcard
Check
Petition for an Extension of Time
Declaration of Davin C. Dillon

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

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VERSION WITH MARKINGS TO SHOW CHANGES

23. A method for detecting prostate cancer in a patient comprising:

(d) obtaining a biological sample from the patient;

(e) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein said ~~at least one of the~~ oligonucleotides ~~is~~ primers are specific for a DNA molecule comprising a sequence selected from the group consisting of SEQ ID NO:110 and complements of SEQ ID NO:110; and

(f) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers thereby detecting prostate cancer, wherein the biological sample is selected from the group consisting of: blood and semen.

24. The method of claim 23, wherein ~~at least one of~~ the oligonucleotide primers comprises at least about 10 contiguous nucleotides of SEQ ID NO:110.

~~25. A method for detecting prostate cancer in a patient comprising:~~

~~(a)obtaining a biological sample from the patient;~~

~~(b)contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for a DNA molecule comprising a sequence selected from the group consisting of SEQ ID NO:111 and complements of SEQ ID NO:111; and~~

~~(c)detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers thereby detecting prostate cancer,~~

~~wherein the biological sample is selected from the group consisting of: blood and semen.~~

~~26. The method of claim 25, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of SEQ ID NO:111.~~

~~27. A method for detecting prostate cancer in a patient comprising:~~

~~(a)obtaining a biological sample from the patient;~~

~~(b)contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for a DNA molecule comprising a sequence selected from the group consisting of SEQ ID NO:115 and complements of SEQ ID NO:115; and~~

~~(c)detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers thereby detecting prostate cancer, wherein the biological sample is selected from the group consisting of: blood and semen.~~

~~28. The method of claim 27, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of SEQ ID NO:115.~~

29. A method for detecting prostate cancer in a patient comprising:

(d) obtaining a biological sample from the patient;

(e) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein ~~at least one of the~~the oligonucleotides primers ~~is~~are specific for a DNA molecule

comprising a sequence selected from the group consisting of SEQ ID NO:173-175, 177 and complements of SEQ ID NO:173-175 and 177; and

(f) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers thereby detecting prostate cancer, wherein the biological sample is selected from the group consisting of: blood and semen.

30. The method of claim 29, wherein ~~at least one of~~ the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a DNA molecule comprising a sequence selected from the group consisting of SEQ ID NO:173-175 and 177.

31. A method for detecting prostate cancer in a patient comprising:

(d) obtaining a biological sample from the patient;

(e) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein ~~at least one of~~ the oligonucleotide primerss ~~is~~ are specific for a DNA molecule comprising a sequence selected from the group consisting of SEQ ID NO:223 and complements of SEQ ID NO:223; and

(f) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers thereby detecting prostate cancer, wherein the biological sample is selected from the group consisting of: blood and semen.

32. The method of claim 31, wherein ~~at least one of~~ the oligonucleotide primers comprises at least about 10 contiguous nucleotides of SEQ ID NO:223.

33. A method for detecting prostate cancer in a patient comprising:

(d) obtaining a biological sample from the patient;

(e) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein ~~at least one of~~ the oligonucleotide primers~~s~~ are~~is~~ specific for a DNA molecule comprising a sequence selected from the group consisting of SEQ ID NO:224 and complements of SEQ ID NO:224; and

(f) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers thereby detecting prostate cancer, wherein the biological sample is selected from the group consisting of: blood and semen.

34. The method of claim 33, wherein ~~at least one of~~ the oligonucleotide primers comprises at least about 10 contiguous nucleotides of SEQ ID NO:224.

35. A method for detecting the presence of a DNA molecule comprising SEQ ID NO: 110 in a biological sample, the method comprising:

(a) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein ~~at least one of~~ the oligonucleotides primers are~~is~~ specific for SEQ ID NO:110; and

(b) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers.

36. The method of claim 35, wherein ~~at least one of~~ the oligonucleotide primers comprises at least about 10 contiguous nucleotides of SEQ ID NO:110.

~~37. A method for detecting the presence of a DNA molecule comprising SEQ ID NO: 111 in a biological sample, the method comprising:~~

~~(a) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for SEQ ID NO:111; and~~

~~(b) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers.~~

~~38. The method of claim 37, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of SEQ ID NO:111.~~

~~39. A method for detecting the presence of a DNA molecule comprising SEQ ID NO: 115 in a biological sample, the method comprising:~~

~~(a) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for SEQ ID NO:115; and~~

~~(b) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers.~~

~~40. The method of claim 39, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of SEQ ID NO:115.~~

41. A method for detecting the presence of a DNA molecule comprising a sequence selected from the group consisting of: SEQ ID NO:173-175 and 177 in a biological sample, the method comprising:

(a) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein ~~at least one of~~ the oligonucleotide primers are~~s is~~

specific for a DNA molecule comprising a sequence selected from the group consisting of: SEQ ID NO:173-175 and 177; and

(b) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers.

42. The method of claim 41, wherein ~~at least one of~~ the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a DNA molecule comprising a sequence selected from the group consisting of: SEQ ID NO:173-175 and 177.

43. A method for detecting the presence of a DNA molecule comprising SEQ ID NO: 223 in a biological sample, the method comprising:

(a) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein ~~at least one of~~ the oligonucleotide primers are~~s is~~ specific for SEQ ID NO:223; and

(b) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers.

44. The method of claim 43, wherein ~~at least one of~~ the oligonucleotide primers comprises at least about 10 contiguous nucleotides of SEQ ID NO:223.

45. A method for detecting the presence of a DNA molecule comprising SEQ ID NO: 224~~115~~ in a biological sample, the method comprising:

(a) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein ~~at least one of~~ the oligonucleotide primers are~~s is~~ specific for SEQ ID NO:224; and

(b) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers.

46. The method of claim 45, wherein ~~at least one of~~ the oligonucleotide primers comprises at least about 10 contiguous nucleotides of SEQ ID NO:224.